

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 334

[Docket No. 1978N-036L]

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DMB

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Certifier J. COOLE

**Laxative Drug Products for Over-the-Counter Human Use; Proposed
Amendment to the Tentative Final Monograph**

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is reopening the administrative record and proposing to amend the tentative final monograph (proposed rule) for over-the-counter (OTC) laxative drug products to reclassify the bulk-forming laxative psyllium ingredients (psyllium (hemicellulose), psyllium hydrophilic mucilloid, psyllium seed, psyllium seed (blond)), psyllium seed husks, plantago ovata husks, and plantago seed)) in a granular dosage form from Category I (generally recognized as safe and effective and not misbranded) to Category II (not generally recognized as safe and effective or misbranded). The granular dosage form affected by this proposal includes, but is not limited to, any granules that are swallowed dry prior to drinking liquid; any granules that are dispersed, suspended, or partially dissolved in liquid prior to swallowing; any granules that are chewed, partially chewed, or unchewed, and then washed down (or swallowed) with liquid; and any granules that are sprinkled over food. FDA is issuing this proposed rulemaking after considering data and information on the safety of some currently

marketed products containing psyllium in a granular dosage form. This proposed rulemaking does not apply to nongranular dosage forms of psyllium, such as powders. FDA has determined that psyllium in a granular dosage form presents an unacceptable safety risk to consumers because esophageal obstruction continues to occur despite currently required label warnings and directions. This proposal is part of FDA's ongoing review of OTC drug products.

DATES: Submit written or electronic comments by [*insert date 90 days after date of publication in the **Federal Register***]; submit written or electronic comments on the FDA's economic impact determination by [*insert date 90 days after date of publication in the **Federal Register***]. See section IX for the effective date of any final rule that may publish based on this proposal.

ADDRESSES: Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Arlene Solbeck, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:

I. Background

In the advance notice of proposed rulemaking (ANPRM) for OTC laxative, antidiarrheal, emetic, and antiemetic drug products (40 FR 12902 at 12906, March 21, 1975), the advisory review panel on OTC laxative, antidiarrheal, emetic, and antiemetic drug products (the Panel) recommended Category I status for the OTC bulk laxative psyllium ingredients, which include plantago

seed, plantago ovata husks, psyllium (hemicellulose), psyllium hydrophilic mucilloid, psyllium seed, psyllium seed (blond), and psyllium seed husks. FDA concurred with the Panel's Category I classification of these ingredients in the tentative final monograph (TFM) published in the **Federal Register** of January 15, 1985 (50 FR 2124 at 2152).

In the ANPRM, the Panel recommended a warning statement (§ 334.52(a)(1) 21 CFR 334.52(a)(1)) for bulk forming laxatives that advised drinking a full glass, 8 ounces (oz), of liquid with each dose and direction statements (§ 334.10(f)) advising adequate fluid intake. The Panel concluded that adequate fluid intake was necessary for the proper use of bulk-forming laxatives because esophageal and intestinal obstruction had occurred from ingesting bulk-forming laxatives with insufficient water or in the presence of certain disease conditions (40 FR 12902 at 12908). FDA discussed the risk of esophageal obstruction from certain bulk laxative ingredients, including water-soluble gums, and the need for adequate fluid intake (8 oz) with each dose in comments 36 and 37 of the TFM (50 FR 2124 at 2131 and 2132). FDA proposed the direction "Drink a full glass (8 oz) of liquid with each dose" to define adequate fluid intake.

In the **Federal Register** of October 1, 1986 (51 FR 35136), FDA amended the TFM and proposed that bulk laxative ingredients be administered in divided doses rather than a single daily dose. The amendment was based on data that indicated the maximum daily dose of some bulk laxatives was so large that it may pose a risk of esophageal obstruction if taken at one time (51 FR 35136).

After receiving reports of cases of esophageal obstruction due to ingestion of laxative products containing water-soluble gums, hydrophilic gums, and

hydrophilic mucilloids, including psyllium, FDA published a proposed rule in the **Federal Register** of October 30, 1990 (55 FR 45782), to require a warning in the labeling of all OTC drug products containing water-soluble gums as active ingredients. FDA added the warning to alert users to take adequate fluid and to avoid using these products if the person had previously experienced any difficulty in swallowing. FDA published a final rule requiring new warning and direction statements in the **Federal Register** of August 26, 1993 (58 FR 45194) and amended that rule in the **Federal Register** of March 17, 1999 (64 FR 13254 at 13292). The current warnings and directions (in § 201.319(b) (21 CFR 201.319(b)) state:

“‘Choking’ [highlighted in bold type]: Taking this product without adequate fluid may cause it to swell and block your throat or esophagus and may cause choking. Do not take this product if you have difficulty in swallowing. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention;” and

“‘Directions’ [highlighted in bold type]:” (Select one of the following, as appropriate: “Take” or “Mix”) “this product (child or adult dose) with at least 8 ounces (a full glass) of water or other fluid. Taking this product without enough liquid may cause choking. See choking warning.”

II. Adverse Events Regarding Psyllium Ingredients in a Granular Dosage Form

A granular dosage form of psyllium, as a single ingredient product or a combination product containing psyllium (82 percent) and senna (18 percent), was introduced into the OTC market around 1979. In 1989, a major manufacturer of psyllium granular dosage form products reported to FDA 61 cases of esophageal obstruction and choking that occurred between February 1980 and December 1988 (Ref. 1). No deaths occurred, but these reports indicated that 19 people were hospitalized and 31 people required medical

intervention in the form of endoscopy to dislodge the esophageal obstructions. The same manufacturer had submitted a comment in 1985 (Ref. 2) to the laxative TFM stating that consumer labeling of psyllium containing laxatives should: (1) State that bulk-forming laxatives have the potential to block the esophagus, particularly in the presence of esophageal narrowing or when consumed with insufficient liquid, (2) bear a warning to drink sufficient amounts of fluid, (3) advise people with esophageal narrowing against using the product, and (4) direct individuals who experience esophageal obstruction, regurgitation, and difficulty swallowing to seek immediate medical attention. In response to the comment (Ref. 3), FDA suggested that the cases of esophageal blockage may be related to the manufacturer's directions for use, which instruct consumers to place the granules in the mouth and swallow, without chewing, prior to drinking liquid. FDA noted that other psyllium-containing OTC laxative drug products are mixed into liquid or food or, in the case of wafers and chewable tablets, chewed before swallowing. FDA indicated that it did not consider the manufacturer's directions for its products adequate to provide for their "safe OTC use" and suggested that, to retain OTC status, the manufacturer should consider reformulating the products to be suspended in "no less than 8 ounces of liquid per dose prior to consumption" or provide more specific labeling information indicating that the product is "not to be taken directly by spoon or swallowed dry." FDA stated that the manufacturer's products might require a new drug application (NDA) for use under medical supervision. FDA mentioned other reports of esophageal obstruction and asphyxiation associated with the ingestion of water-soluble gums, hydrophilic gums, and hydrophilic mucilloids, including psyllium.

In response to FDA's concerns (Ref. 4), the manufacturer noted that it took the following actions to resolve the problems of esophageal obstruction and choking: (1) In 1985, the directions for use were modified to emphasize the need to have adequate fluid intake, (2) a patient package insert was placed inside each package stressing the importance of taking sufficient liquid, and (3) a "dear doctor" letter was issued in February 1985 to U.S. physicians calling attention to the need for adequate fluid intake to avoid the risk of esophageal obstruction. The manufacturer stated that only 15 of the 61 cases occurred after it took these actions.

As noted previously, on August 26, 1993, FDA published a final rule in the **Federal Register** requiring warning and direction statements in the labeling of all OTC drug products containing water-soluble gums as active ingredients, including psyllium. Additional warnings and directions were added to alert users to consume adequate fluid and to avoid using such products if the person had previously experienced any difficulty in swallowing.

Despite the new required warnings and directions and other labeling changes initiated by the manufacturer, FDA continued to receive reports of choking and esophageal obstruction associated with psyllium, particularly the granular dosage form. In November 2000, FDA reviewed reports (postmarketing safety review) from its adverse event reporting system (AERS) database and the medical literature for the time between 1966 and 2000 (Ref. 5). FDA identified 98 reported cases of esophageal obstruction and choking associated with the use of psyllium products (Ref. 6). Four deaths occurred and 66 cases required medical intervention and/or hospitalization. Of these 98 cases, 78 (80 percent), including 1 death and 59 cases that required medical intervention and/or hospitalization, were related to the granular dosage form that is

swallowed unchewed while drinking liquid. Medical intervention included endoscopy (in 41 cases), esophageal dilatation, surgery, nasogastric tube, Heimlich maneuver, and polypectomy snare. The mean age in these cases (27 cases not reporting age) was 69 years. Possible risk factors were identified in 52 percent of the cases, although there were 37 cases with no reported or apparent risk factors.

FDA also identified 13 (11 percent) cases of choking-related events (and two cases of esophageal obstruction (2 percent)) related to a powder or wafer psyllium product. The label of these products stated that the powder should be mixed with 8 oz of liquid and the wafers should be consumed with 8 oz of liquid. The mean age in these cases was 71 years. There were three deaths (two from asphyxiation and one from bronchus obstruction) and seven people who required hospitalization. Three cases (4 percent) of choking and/or difficulty swallowing and four cases (5 percent) of esophageal obstruction were related to the use of another psyllium product available as a powder or toasted granules. The product directions indicated to mix the powder with liquid and sprinkle the granules on food. All seven cases (mean age was 64 years) required hospitalization.

Although these reports indicate there were fewer deaths related to the granular dosage form that was swallowed unchewed while drinking liquid (one out of four), there were significantly more overall cases of esophageal obstruction (78 out of 98) and cases that required medical intervention (59 out of 66) with this dosage form.

In January 2001, FDA requested and obtained updated adverse event reports from a current major manufacturer of psyllium laxative products in granular dosage form for the time period between January 1999 and January

2001 (Ref. 7). In April 2002, FDA received an update from this manufacturer for the time period after January 2001 (Ref. 8). This manufacturer's product labeling contained the following directions:

(1) Moisten your mouth with a drink of water or any cool beverage, (2) Place a teaspoonful of granules on your tongue. If you prefer, take only a partial teaspoonful at a time, (3) Without chewing, wash granules down with water or any cool beverage, (4) Repeat steps 1–3 until the recommended dose has been swallowed. Be sure to drink at least 8 ounces of cool liquid.

FDA's reviews (Refs. 9 and 10) of these reports identified 44 additional cases of adverse events related to esophageal obstruction between January 1999 and May 2002. No deaths were reported, but 13 of the reported cases were considered serious events requiring medical intervention (11 underwent endoscopy). The adverse event reports suggested that most of the people using the products followed the directions on the label (information on the dose taken was available in 36 out of 44 cases). Most people (27 out of 35) took sufficient fluid with the product, while insufficient fluid intake may have contributed to the esophageal obstruction in 7 cases.

In summary, FDA has received 142 cases of adverse events regarding esophageal obstruction and choking associated with psyllium between 1966 and May 2002. Of these 142 cases, 59 occurred after publication of the 1993 required warning (58 FR 45194) with 45 reported to have occurred during the last 3 years alone. Eleven of these 45 reported cases (25 percent) involved hospitalization and/or the need for invasive procedures.

Based on the data reviewed, and despite the warnings it has mandated, FDA now believes that there still exists a significant safety problem with esophageal obstruction associated with psyllium laxative products in granular

dosage form, particularly products that are swallowed dry, swallowed partially moistened prior to drinking liquid, and swallowed unchewed while drinking liquid. FDA is concerned that a consumer ingesting this granular dosage form is less likely to drink adequate amounts of fluid with the product than a consumer instructed to mix the product in 8 oz of fluid prior to ingestion. Multiple labeling changes, including additional warnings and enhanced directions to take adequate fluid, have not alleviated this problem. Rather, the problem seems to have worsened. During the first 10 years of marketing, 61 cases of esophageal obstruction were reported compared to 44 cases during the last 3 years alone. In addition, FDA is concerned that the incidence of serious adverse events for these products is underreported because reporting for products marketed under an OTC drug monograph is not currently mandatory.

III. FDA's Tentative Conclusion on OTC Psyllium Ingredients in a Granular Dosage Form

FDA now considers OTC laxative drug products containing psyllium ingredients in granular dosage form as presenting an unacceptable health risk to consumers. These drug products include, but are not limited to: (1) Any granules that are swallowed dry prior to drinking liquid, (2) any granules that are dispersed, suspended, or partially dissolved in liquid prior to swallowing, (3) any granules that are chewed, partially chewed, or unchewed, and then washed down (or swallowed) with liquid, and (4) any granules that are sprinkled over food.

FDA continues to receive reports of esophageal obstruction and choking associated with these products despite the warning and direction statements required for all water soluble gums in § 201.319. Therefore, due to the significant safety risk these products pose, FDA is proposing to reclassify bulk

laxative psyllium ingredients in granular dosage form from Category I (monograph) to Category II (nonmonograph). FDA proposes to add these ingredients in granular dosage form to the list of bulk laxatives in § 310.545(a)(12)(i) (21 CFR 310.545(a)(12)(i)) and to amend proposed § 334.10 (bulk-forming laxative active ingredients) to exclude the granular dosage form.

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not find so. Nor does FDA's requirement of warnings repudiate the prior OTC drug regulations and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act (the act). This judgment balances the benefits of these drug products against their potential risks (see § 330.10(a) 21 CFR 330.10(a)). In the current situation, FDA has determined that warnings are not adequate to address the significant safety risks that these products pose.

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals, Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see "Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use, final rule" (67 FR 72555, December 6, 2002).

Accordingly, if a final rule based on this proposal issues any drug product containing any psyllium ingredients in granular dosage form will be considered nonmonograph and misbranded under section 502 of the act (21 U.S.C. 352). This type of drug product would also be considered a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355), and set forth in part 314 of the regulations, is required for marketing. If a final rule is based on this proposal issues, it would apply to any OTC drug product containing psyllium ingredients in granular dosage form that is initially introduced or initially delivered for introduction into interstate commerce after the effective date of the final rule. Further, any OTC drug product that was previously initially introduced or initially delivered for introduction into interstate commerce could not then be repackaged or relabeled after the effective date of the final rule.

IV. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–12), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act

of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by state, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

FDA believes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. The proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for this proposed rule, because the proposed rule is not expected to result in any 1-year expenditures that would exceed \$100 million adjusted for inflation. The current inflation adjusted statutory threshold is about \$110 million.

The purpose of this proposed rule is to establish conditions under which OTC bulk-forming laxative psyllium ingredients in a granular dosage form are not generally recognized as safe and effective. FDA's drug listing system (DLS) identifies nine currently marketed OTC laxative drug products containing psyllium ingredients in granular dosage form and FDA is aware of at least one other product not in its DLS. One manufacturer currently markets three stock keeping units (SKUs) (individual products, packages, and sizes) of the granular dosage form that requires the product to be swallowed dry while drinking liquid; two manufacturers market two SKUs each, and one manufacturer markets one SKU. It is likely that there may be a few additional products that are currently not included in FDA's DLS. This proposed rule, when finalized, will result in the reformulation or removal of probably less than a dozen products.

- Reformulation Costs

Some manufacturers may elect not to reformulate (i.e., they may elect to discontinue marketing of the product). For those products that need reformulation, the cost can be significant. The cost to reformulate a product will vary greatly depending on the nature of the change in the formulation, the product, the process, and the size of the firm. A manufacturer may elect to change the dosage form of the psyllium product or to substitute other monograph ingredients. This would require the manufacturer to redo the validation (product, process, new supplier), conduct stability tests, change master production records in order to insure compliance with good manufacturing practice, and, for some dosage forms, conduct palatability tests. (See section 501(a)(1)(B) of the act (21 U.S.C. 351(a)(1)(B) and 21 CFR parts 210 and 211.) FDA estimates the cost of reformulation to range from \$100,000 to \$500,000 per product. Therefore, if 10 products are reformulated, the midpoint of the cost estimate implies total costs of \$3,000,000. However, FDA believes the total costs will be much smaller because not all manufacturers will elect to reformulate and some may choose to discontinue a product line if sales are too low to justify the added cost, and/or they also produce substitute products that do not require reformulation. Manufacturers may also elect to purchase reformulated products from another manufacturer and then be a distributor of that product. Competitive market forces and increased public awareness of a potential safety hazard of these ingredients in a granular dosage form would most likely lead all manufacturers to move to alternative products over time.

- Relabeling Costs

Manufacturers of these products will also incur costs to relabel their products to reflect the new formulation. Estimates of relabeling costs vary greatly and range from \$3,000 to \$5,000 per SKU depending on whether the products are nationally branded or private label. FDA estimates that manufacturers with more than one affected SKU will likely discontinue one or more SKUs. If some SKUs are discontinued, FDA estimates that only three to six SKUs will need to be relabeled as a result of reformulation. If these SKUs are relabeled, the total one-time cost of relabeling could range from \$9,000 (three SKUs x \$3,000) to \$30,000 (six SKUs x \$5,000). This relabeling cost should not be a significant economic impact on a substantial number or small entities.

Some manufacturers may choose to submit an NDA deviation for their psyllium product in accordance with § 330.11. Overall, there may be fewer costs incurred by this process than by submission of a full NDA.

Because these products must be manufactured in compliance with the pharmaceutical current good manufacturing practices (21 CFR parts 210 and 211), all firms have the necessary skills and personnel to perform the tasks of reformulation, validation, and relabeling either in-house or by contractual arrangement. The rule will not require any new reporting and recordkeeping activities. No additional professional skills are needed.

- Regulatory Alternatives Considered

FDA considered but rejected the following additional alternatives: (1) Leave these products in the monograph, and (2) an exemption from coverage for small entities. FDA does not consider either of these approaches acceptable because they do not assure that consumers will have safe OTC psyllium laxative drug products in a granular dosage form. FDA does not believe that

there are any significant alternatives to the proposed rule that would adequately provide for the safe use of these OTC drug products.

FDA does not believe that this proposed rule would have a significant economic impact on a substantial number of small entities. However, FDA recognizes the uncertainty of its estimates with respect to the number of affected small entities and products, as well as the economic impact of the rule on those small entities. Thus, this economic analysis, together with other relevant sections, serves as FDA's initial regulatory flexibility analysis.

Finally, FDA specifically invites public comment regarding any substantial or significant economic impact that this proposed rule would have on OTC laxative drug products containing psyllium ingredients in a granular dosage form. Types of impact may include, but are not limited to, the costs associated with reformulation, relabeling, or repackaging. Comments regarding the impact of this rulemaking on OTC laxative drug products containing these ingredients should be accompanied by appropriate documentation. FDA is providing a period of 90 days from the date of publication of this proposed rule in the **Federal Register** for comments on this subject to be developed and submitted. FDA will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

V. Paperwork Reduction Act of 1995

FDA tentatively concludes that any relabeling resulting from this proposed rule is not subject to review by the Office of Management and Budget because it does not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the relabeling statements are in the TFM for OTC laxative drug products (50 FR 2124 and

51 FR 35136) and are a “public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public” (5 CFR 1320.3(c)(2)).

VI. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, FDA tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order, and, consequently, a federalism summary impact statement has not been prepared.

VIII. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

IX. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal become effective 180 days after its date of publication in the **Federal Register**.

X. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) under Docket No. 78N–036L, unless otherwise noted, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Adverse Drug Reaction Reports, Ref. 7 in OTC vol. AF, Docket No. 90N–0200, Division of Dockets Management.
2. Comment No. C00100.
3. Comment No. LET45.
4. Comment No. LET46.
5. Adverse Event Reports from 1966 to 2000 for Psyllium Laxative Products (Perdiem, Metamucil, and Serutan) collected by FDA’s Office of Compliance, in OTC vol. 090TFM6.
6. FDA, Office of Postmarketing Drug Risk Assessment (OPDRA) (Project ID (PID) 000607) regarding Psyllium Laxative Products Associated with Esophageal Obstruction and Choking, November 17, 2000, in OTC vol. 090TFM6.
7. Adverse Event Reports from January 1999 to January 2001 for Overnight Relief PERDIEM and Fiber Therapy PERDIEM collected by FDA’s Office of Compliance in January 2001, in OTC vol. 090TFM6.
8. Adverse Event Reports from October 2000 to January 2002 for Overnight Relief PERDIEM and Fiber Therapy PERDIEM collected by FDA’s Office of Compliance in April 2002, in OTC vol. 090TFM6.
9. FDA, Cases of Esophageal Obstruction Associated with PERDIEM (January 1999 to January 2001), in OTC vol. 090TFM6.

10. FDA, OPDRA Postmarketing Safety Review (PID D020201) regarding Senokot and Psyllium Laxative Products Associated with Esophageal Obstruction and Choking, May 15, 2002, in OTC vol. 090TFM6.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 334

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 310 and 334 (as proposed in the **Federal Register** of January 15, 1985 (50 FR 2124), October 1, 1986 (51 FR 35136), September 2, 1993 (58 FR 46589), March 31, 1994 (59 FR 15139), September 2, 1997 (62 FR 46223), May 21, 1998 (63 FR 27886), and June 19, 1998 (63 FR 33592)), be amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e, 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.545 is amended by redesignating paragraph (a)(12)(i) as paragraph (a)(12)(i)(A), by adding new paragraph (a)(12)(i)(B), by revising paragraph (d) introductory text and paragraph (d)(1), and by adding new paragraph (d)(38) to read as follows:

§ 310.545 Drug products containing active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(12) * * *

(i)(B) *Bulk laxatives*—Approved as of [date of publication] in the **Federal Register**].

Psyllium (hemicellulose), psyllium hydrophilic mucilloid, psyllium seed, psyllium seed (blond), psyllium seed husks, plantago husks, plantago seed, in a granular dosage form including, but not limited to any granules that are:

(1) Swallowed dry prior to drinking liquid,

(2) Dispersed, suspended, or partially dissolved in liquid prior to swallowing,

(3) Chewed, partially chewed, or unchewed, and then washed down (or swallowed) with liquid, or

(4) Sprinkled over food.

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(38) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3)(i), (a)(4)(i), (a)(6)(i)(A), (a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), paragraphs (a)(8)(i), (a)(10)(i) through (a)(10)(iii), (a)(12)(i)(A), (a)(12)(ii) through (a)(12)(iv)(A), (a)(14) through (a)(15)(i), (a)(16) through (a)(18)(i)(A), (a)(18)(ii) (except as covered by paragraph (d)(22) of this

section), paragraphs (a)(18)(iii), (a)(18)(iv), (a)(18)(v)(A), and (a)(18)(vi)(A) of this section.

* * * * *

original rule *Read Brooks.*

(38) [Date 180 days after date of publication in the **Federal Register**], for products subject to paragraph (a)(12)(i)(B) of this section.

PART 334—LAXATIVE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 334 continues to read as follows:

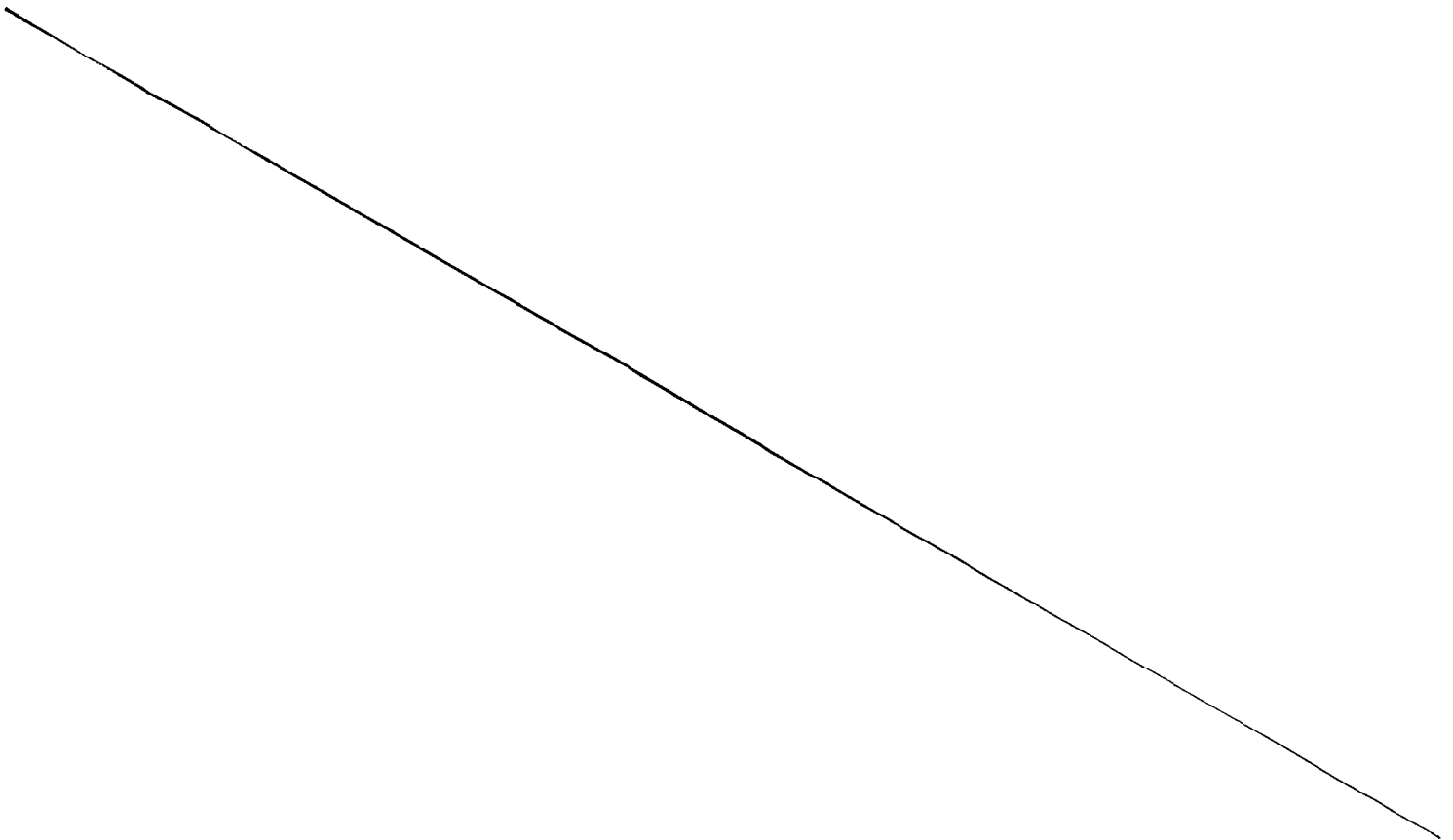
Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

§ 334.10 [Amended]

as proposed January 15, 1985 (50 FR 2124), is proposed to be further

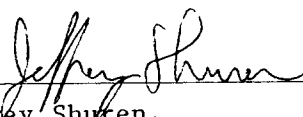
4. Section 334.10 *Bulk-forming laxative active ingredients* is amended by revising paragraph (f) to read as follows:

* * * * *




(f) Psyllium ingredients, except those listed in § 310.545(a)(12)(i)(B) of this chapter.

Dated: 7/25/03
July 25, 2003.



Jeffrey Shuren,
Assistant Commissioner for Policy.

CERTIFIED TO BE A TRUE
COPY OF THE ORIGINAL



J. Cooke

[FR Doc. 03-????? Filed ??-??-03; 8:45 am]

BILLING CODE 4160-01-S